Contents

Chapter 1 **An Aproach to a Dysmorphic Child** **1**
Sheela Nampoothiri
Purpose of Genetic Evaluation in a Dysmorphic Child 2
Evaluation of a Dysmorphic child 2
Description of Common Terminologies Depicting Facial Anomalies 6
Diagnosis 9

Chapter 2 **The Genetics of Overgrowth Syndromes** **13**
Koumudi Godbole
Molecular Aspects 14
Genomic Imprinting and UPD 14
Uniparental Disomy (UPD) 15
Genes Associated with Common Overgrowth Syndromes 15
Approach to a Clinical Diagnosis of "Overgrowth" 21
Physical Examination 21
Investigations 22
Management 22

Chapter 3 **An Approach to the Diagnosis of Skeletal Dysplasias** **25**
Meenakshi Bhat
Osteogenesis 28
Chondrogenesis 29
Common Disorders in Each Group 29

Chapter 4 **Application of Chromosome Study in Different Clinical Settings: An Overview** **37**
Frenny Sheth
What is Cytogenetics 37
Chromosomal Anomalies are Mainly of Two Types 40
Numerical Anomalies 41
Sex Chromosomal Anomalies 43
Cytogenetic Study in Multiple Congenital Anomalies/Dysmorphic Features with/without Mental Retardation 44
Cytogenetic Study in Couples with Repeated Fetal Loss 47
Cytogenetic Study in Infertility 47
Cytogenetic Study in the Product of Conception (Abortus Material) 50
Cytogenetically Detectable Small Supernumerary Marker Chromosome (sSMC) 52
Cytogenetics Study in Prenatal Diagnosis 56
Cytogenetic Study in Cancer 59
Chromosome Study in Instability Syndromes 60

Chapter 5 **Fluorescence *In Situ* Hybridization (FISH): When and How to Do? How to Interpret? How to Counsel? 73**
Thomas Liehr
What is Molecular Cytogenetics? 74
Probes and Probe Sets Used in FISH 76
Application of FISH in General 78
FISH in Prenatal Cases 80
FISH in Postnatal Cases 83
FISH after a Positive Cytogenetic Result 88
FISH after a Positive UPD-Diagnostics 88
FISH after a Positive or Negative Array-CGH Diagnostics 88

Chapter 6 **Array-Comparative Genomic Hybridization (a-CGH) in Constitutional and Acquired Anomalies 93**
Frenny Sheth, Joris Andrieux
What is Comparative Genomic Hybridization (CGH) 94
Types of Array 94
When to Use Array- CGH (a-CGH) as a Diagnostic Tool 96
Application of a-CGH in Clinical Genetics 97
Application in Recognition of Known and Unknown Chromosomal Syndrome 97
Application to Recognize New Genetic Defects in a known Syndrome 100
Application to Identify the Incidence of Mosaicism 100
Application of Copy Number Variant Across the Genome 101
Application in Autism Spectrum Disorders (ASD) 101
Application in Characterization of Small Supernumerary Marker Chromosome (sSMC) 102
Application in Prenatal Cases 105
Application in the Product of Conception 106
Application in Oncohematology and Tumors 108

Chapter 7 **Molecular Genetics of α and β Thalassemia and Sickle Cell Disease 115**
Roshan Colah, Anita Nadkarni, Ajit Gorakshakar
Chromosomal Localization and Structure of the Globin Gene Clusters 115
Globin Gene Regulation 116
β-Thalassemias 117
Molecular Defects in β-Thalassemia 118
β-Thalassemic Hemoglobinopathies 119
δβ Thalassemia 120
β Thalassemia Mutations in Indians 120
Prenatal Diagnosis 121
α Thalassemias 122
Deletional α^+ Thalassemia 122
Non-deletional α^+ Thalassemia 123
Deletional α^0 Thalassemia 123
Carriers of α Thalassemia 125
α Thalassemia Mutations in India 125
α Gene Triplication 126
α Thalassemia/Mental Retardation Syndrome 126
Sickle Cell Disease 126
Pathophysiology 127

Clinical Manifestations 127
Co-inheritance of α-Thalassemia 129
β-Globin Silencer 129
Non-Globin Genetic Modifiers 130

Chapter 8 **Molecular Genetics of Hemophilia A and B** **136**
Shrimati Shetty
Structure of Factor VIII (*F8*) and Factor IX (*F9*) Genes 137
Genetic Diagnosis of Hemophilia A and B 138
Methods for Detection of Intron 22 Inversions 138
Mutation Screening Techniques 140
Phenotypic Investigations 148
Modulation of Clinical Severity by Co-inherited Thrombophilia 148
Multiple Mutations 149
Genetic Counseling 149

Chapter 9 **Duchenne Muscular Dystrophy: Symptoms, Diagnosis and Therapy** **153**
Seema Thakur, Sudha Kohli, Renu Saxena
Brief History 154
Clinical Features of Duchenne Muscular Dystrophy 154
Diagnostic Evaluation in Dystrophinopathies 156
Management and Treatment 162
Prevention and Genetic Counseling 168

Chapter 10 **Usefulness of Gas Chromatography and Mass Spectrometry in Metabolic Medicine** **175**
Anil B Jalan, Ketki Kudalkar, Rishikesh Jalan
Indication for GC-MS Analysis 176
Conflict of Interest 184

Chapter 11 **Prenatal Screening for Down Syndrome and Other Aneuploidies** **186**
Prakash Gambhir
What is a Marker and How are the Markers Identified? 187
Multimarker Screening Stratgies 194
Future of Prenatal Screening 198

Chapter 12 **Lysosomal Storage Diseases: Symptoms, Diagnosis and Counseling** **202**
Jayesh Sheth
Physiological Considerations of Lysosomal Storage Disorders 204
When to Suspect a Child with LSDs 207
Other Clinical Considerations for LSDs 207
Inclusion-Cell Screening by Chemical Method 210
Clinical Cases of LSDs 215
Hurler Disease (MPS I H) 216
Hurler-Scheie (MPS I H-S) 216
Hunter Disease (MPS II) 217
Sanfilippo Type A (MPS III A) 217
Morquio Disease Type A (MPS IV A) 217

Maroteaux-Lamy Syndrome (MPS VI) 218
Sly Syndrome (MPS VII) 218
Gaucher Disease Type I 219
Tay-Sachs Disease 219
GM1 Gangliosidosis 220
Inclusion-Cell Disease Mucolipidosis II 220
Niemann-Pick Disease B (NPD B) 220
Niemann-Pick Disease Type-C (NPD-C) 221
Krabbe Disease 221
Prenatal Diagnosis of Lysosomal Storage Disorders 221
Treatment for LSDs 222

Chapter 13 **Neural Tube Defects: Cause and Prevention in India** **229**
Koumudi Godbole
Incidence of NTDs 229
Genetic Contribution 234
Consanguinity 234
Genetic Susceptibility 234
Animal Models 234
Prevention of NTDs 235
Nutritional Supplementation 235
Prenatal Diagnosis and Management of NTDs 236
Fetal Surgery 237
Postnatal Management 237

Chapter 14 **Quality Issues in Medical Genetics** **239**
Prajnya Ranganath, Ashwin Dalal
Quality Control in Clinical Practice 240
Quality Control in Genetic Testing 241
Regulation of Genetic Testing 244
Direct-to-Consumer Testing 244

Index *247*